

**ACUTE LYPHOCYTIC (LYMPHOBLASTIC) LEUKEMIA
FALLON, NEVADA**

**REVIEW AND RECOMMENDATIONS
OF THE
EXPERT PANEL**

February 15, 2001

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The expert panel was convened on February 15, 2001 in Reno, Nevada by Dr. Mary Guinan, Nevada State Health Officer. The panel reviewed the Nevada State Health Division's investigation of acute lymphocytic (lymphoblastic) leukemia (ALL) cases that had been diagnosed in Churchill County, Nevada. The panel considered possible follow-up actions and priorities by the Nevada Health Division. The meeting of the expert panel was attended by panel members and staff from the Nevada Health Division, University of Nevada School of Medicine, Nevada Governor's Office, U.S. Senate (Senator John Ensign's Office and Senator Reid's staff on U.S. Senate Committee on Environment and Natural Resources), and the Fallon Naval Air Base. This report summarizes the panel's review and recommendations.

The expert panel recognized the difficulty in evaluating and investigating excess occurrences of ALL. The panel members acknowledged that the cause(s) of ALL are insufficiently understood to single out a specific factor as explaining the observed excess in Fallon, Nevada. The panel members were familiar with previous investigations of ALL clusters, all of which had failed to uncover an explanation of the cause of these excesses. At the same time, the panel members confirmed that the excess occurrence of ALL in Fallon, Nevada is unusual; not only because of its large number of observed cases among so small a population-at-risk over a short time period, but also because further observed ALL cases had been diagnosed after the initial recognition of the ALL excess. The members of the expert panel acknowledged the excellent work of the staff of the Nevada Health Division on this investigation.

Scientific understanding of the biology of ALL prevented the committee members from predicting the cause of the observed excess of cases in Fallon. The committee is aware of at least three distinct sets of possibilities. The first set of theories collectively point toward a cancer

causing chemical contaminant (e.g., human carcinogen) as the causal agent for the ALL epidemic. Theories about a chemical in the environment have received the greatest amount of public attention and community concern. The expert panel recognizes the need to address community concern regarding the presence of a hazardous chemical contaminant. However, the absence of cases of acute myeloid leukemia, the type of leukemia most commonly associated with toxic chemical exposure (1-3), argues against the Fallon cases being the result of toxic exposures. The panel members were skeptical that a chemical exposure could explain the excess cases of ALL in Fallon, Nevada. A second possible explanation relates to the theory of what is called *population mixing* in which clusters of ALL have been reported associated with unusual mixing of people, often in relatively isolated rural areas (4-11). The population mixing theory initially focused on the possibility of an unidentified infectious agent (i.e., a virus). However, the current consensus is that exposure to a variety of infectious agents (i.e., viral and bacterial) may trigger an unusual and rare reaction that affects a very small number of children within the susceptible population. The hypothesis suggests that ALL is not infectious, spreading from one person to another; but an unusual complication to a common infection within a susceptible population. The population-mixing theory is supported by the observation that excesses of ALL eventually subside, presumably because of increased population immunity. This theory requires further examination. The panel believes it reasonable to test this hypothesis by calculating rates of ALL in other rural areas of the U.S. having significant population mixing. However, such an effort falls outside the mandate of the Nevada Health Division. Finally, the possibility that the excess of ALL cases is due to random chance cannot be totally excluded as an explanation. The panel acknowledges, however, that the excess of ALL cases in Fallon, Nevada is not likely to represent a “chance”

occurrence.

The expert panel recommends to the Nevada Health Division six follow-up steps in the investigation of the excess occurrence of ALL in Fallon, Nevada (see Table 1).

The purpose of these next steps are to: 1) efficiently expand case-finding efforts, 2) categorize the observed ALL cases by clinically relevant disease biomarkers, 3) identify potential excess environmental exposures unique to the community by a cross-sectional exposure assessment of **selective** contaminants and an evaluation of contaminant releases into the local environment with assessment of completed pathways for the case families, 4) collect and bank biologic specimens for future scientific investigations, 5) determine the time course and characteristics of population movements into the Fallon area for the period 1990 to 2000, and 6) maintain an expert panel to peer review investigative protocols and study results, consider future use of banked specimens, and provide ongoing consultation to the Nevada Health Division.

The expert panel also discussed the importance of high concentrations of arsenic in municipal and private drinking water supplies. The panel members expressed doubt that arsenic consumption in drinking water, by itself, could explain the observed ALL excess for several reasons: 1) The excess occurrence of ALL began in 1999, whereas the arsenic concentrations in drinking water have been consistently elevated for many years. 2) The case children who make-up the excess occurrence of ALL differ in respect to their consumption of arsenic contaminated drinking water. 3) Epidemiologic studies of arsenic exposed populations have not linked arsenic exposure with adult or childhood leukemia. One recent article suggests a weak association between childhood leukemia risk and exposure to low levels of arsenic in drinking water (12). The panel has reviewed the article and believes that the study is inadequate to support a

conclusion that ALL is related to arsenic in drinking water. Each panel members expressed concern that the ongoing exposure to excess levels of arsenic in drinking water was a human health hazard, regardless of its relationship to the excess of ALL. The Fallon municipal water supply is contaminated with arsenic (As) at a level 10 times the EPA recommended standard for arsenic in drinking water. The panel was also aware that an unknown proportion of Churchill County drinking water wells, unregulated by the federal Safe Drinking Water Act (SDWA), are at least as contaminated as the Fallon municipal water supply. Arsenic is recognized by the Report on Carcinogens of the National Toxicology Program as a known human carcinogen on the basis of epidemiologic studies that have linked arsenic exposure with an excess of skin, bladder, and lung cancers in exposed human populations.

The expert panel recommends that arsenic concentrations in the Fallon municipal drinking water be reduced to a level no more than that currently recommended by EPA (e.g.; 10 ug/L) as soon as possible. The panel strongly encourages the Nevada Health Division, and other state agencies, to proceed with recommendations for testing arsenic in all drinking water wells in Churchill County that are unregulated by the SDWA. The state health division should work to create a process providing this service when necessary and develop a set of recommendations for preventing arsenic exposure based on reported test results. The state health division should consider maintaining a listing of wells that have been tested along with test results.

Table 1: Investigating the excess occurrence of Acute Lymphocytic (Lymphoblastic) Leukemia in Fallon, Nevada: Phase II Recommendations of the Expert Panel (February 15, 2001)

Priority Task / Time frame / Collaborators

1. Efficiently expand case-finding efforts. The panel members encourage the Nevada Health Division to continue limited case-finding strategies. The panel members recommended limited expansion of case-finding by linking to:

- A. The national Childhood Oncology Group (COG) databases(s) to identify all children with ALL having a residence at time of diagnosis in the state of Nevada. The purpose of this would be to evaluate completeness of the Nevada tumor registry and identify additional ALL cases from Churchill County.
- B. An ongoing case-control study of ALL being conducted in California to review residential history of cases for previous residence in Churchill County, Nevada.
- C. The California State Tumor Registry to identify any children with ALL with a Nevada residence at time of diagnosis.

Time frame - these additional steps could be done within two months after satisfactory negotiations regarding patient confidentiality are completed.

Potential Collaborators - Clinical Oncology Group, California Tumor Registry, California ALL research team.

2. Categorize the observed ALL cases by clinically relevant disease biomarkers. Cancer cells from each case-child have probably been collected and undergone immunophenotyping

and cytogenetic testing. The health division should collect this information. If testing has not been done and tumor cells have been stored, the health division should secure samples and have them tested. These materials could be reviewed or tested at two independent laboratories. The distribution of these results among the case-children from Fallon can be compared against other children with ALL to determine if these distribution are similar or if the distribution among the Fallon case-series is unique.

Time frame: The health division should proceed to determine availability of data or tumor cells as soon as possible.

Potential Collaborators: Pediatric oncologists, Childhood Oncology Group, National Cancer Institute.

3. Identify potential excess environmental exposures unique to the community. The health division should conduct limited testing for current exposures in environmental media or human samples as well as evaluate contaminant releases into the local environment and assess the potential for human exposure to such contaminants. This analysis would be used to identify chemicals that are (and are not) elevated in the community and to consider if additional data collection is required.

A. A cross-sectional exposure assessment of **selective** contaminants would include examination of drinking water, human blood and urine of family members, and possibly dust collected from homes where case-children did and did not live. Testing should be limited to compounds for which normative data are available. The expert panel recommended testing for volatile organic compounds in drinking water and human tissues;

radioactive isotopes in drinking water; selected heavy metals in drinking water, household dust, and human tissues; and pesticides in human tissues and in household dust.

B. An evaluation of contaminant releases into the local environment with assessment of completed pathways for the case families. The expert panel recommends collecting environmental release data, including that from local industry and the Fallon Naval Air Station. An assessment of the potential for environmentally released chemicals to result in human exposure should also be conducted, including potential for case-children to have been exposed.

Time frame: These activities will require development of survey and sampling protocols and appropriate review of consent forms and confidentiality agreements. The committee anticipates start-up of these activities during the months of March or April and available results within 1 year.

Potential Collaborators:: National Center for Environmental Health, Centers for Disease Control and Prevention; Agency for Toxic Substances and Disease Registries; Jonathan Buckley (University of Southern California) for input on measuring house dust for pesticide residues, heavy metals, PAHs..

4. Collect and bank biologic specimens for future scientific investigations. The members of the panel recognize how limited our knowledge is of the cause(s) of ALL and the difficulty investigators have had in identifying the causes of similar ALL excesses. The panel members believe that collection of biologic specimens from case-children and family members may be useful for future research investigations into the cause(s) of ALL. A

small amount of blood and urine, and perhaps buccal cells, should be collected, maintained, and made available for future research.

Time frame: Collection of specimens could occur simultaneously with the exposure assessment (see 3A) or include samples taken during clinical care. A protocol for collection, storage, and access to samples must be developed and reviewed by an Institutional Review Board for compliance with human subject research.

Potential Collaborators: Nevada Public Health Laboratory, National Center for Environmental Health, Centers for Disease Control and Prevention, National Cancer Institute as possible repositories for the tissue bank.

5. Determine the time course and characteristics of population movement into the Fallon area for the period 1990-2000. The expert panel recommends collecting demographic data concerning changes in the population of Fallon, specifically looking for evidence of large migration of new long-term residents into the community during this time period. The appended table illustrates the kind of first-level information that is relevant to this issue.

Time frame: initial data collection within two months.

Potential Collaborators: Public school systems and Fallon Naval Airbase (for information concerning migration patterns), Drs Les Robison and Malcolm Smith (for consultation to identify the specific data required).

6. Maintain the expert panel to peer review investigative protocols and study results, review proposals for future use of banked specimens, and provide ongoing consultation to the

Nevada Health Division.

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Appendix I: Recommended* Data to Evaluate Population Dynamics in Fallon, NV

Estimated Populations within Groups	0	1	2	3	4	5	6	7	8	9	0
Population Total											
Individuals <21 yrs											
Individuals <10 yrs											
Military Base personnel Total											
Permanent (>6 mos)											
Temporary (≤ 6 mos)											
Dependents (total)											
Dependents <20 yrs of age											
School Enrollment (Total) K-12											
Elementary (Total)											
Middle School (Total)											
High School (Total)											
Total K-12 (Naval dependents)											
Elementary (Naval dependents)											
Middle School (Naval dependents)											
High School (Naval dependents)											

*It is recognized that the figures requested may not be available for all categories and/or years. Although the objective would be to obtain the most detailed and accurate information possible, crude estimates would be preferable to no information. Accordingly, it will be important to document the level of confidence (i.e., accuracy) for the various pieces of information obtained.